A PHARMACEUTICAL COMPOSITION CONTAINING AN ACTIVE AGENT HAVING THE EFFECT OF DIGITALIS AND A CGMP PHOSPHODIESTERASE INHIBITOR

The invention refers to a cardiotonic pharmaceutical composition having enhanced therapeutical width of effect.

Active ingredients having the effect of digitalis has been used for a very long time as a cardiotonic drug in cases when the heart function is weak, the activity of the myocardium is insufficient, consequently, the heart contractions are forceless. The active ingredients having the effect of digitalis inhibit the sarcolemmal Na^+/K^+-ATPase of the heart myofibrils, thus, enhance the free intracellular calcium concentration required for the contraction. In this way, a positive inotropic effect is obtained.

A drawback of the administration of the active ingredients having the effect of digitalis resides in the fact that it can easily result in arrhythmia. This symptom is due to partly the reduction of the refractoriness of the ventricle myofibrils, partly the occurence of late after-potentials. The arrhythmias are separated ventricular extrasystoles, at first bigeminy, later severe ventricular tachycardia develops. The active ingredients having the effect of digitalis are characterized by a rather narrow therapeutical width, i.e. the difference between the positive inotropic dose (that is the therapeutical dose) and the arrhythmogenic dose is low. In other words, the therapeutical dose lies near to the dose that causes serious arrhythmias.

The aim of the invention is to provide a cardiotonic pharmaceutical composition having an enhanced therapeutical width, thus, the administration of the composition eliminates the development of arrhythmia.

It was found that the above aim is achieved by the pharmaceutical composition of the invention comprising (a) an active ingredient having the effect of digitalis and (b) a cyclic guanosine monophosphate (cGMP) phosphodiesterase inhibitor and one or more conventional carrier(s).

The invention is based on the recognition that in the presence of a cGMP phosphodiesterase inhibitor the cGMP phosphodiesterase enzyme fails to decompose the cyclic guanosine monophosphate present, and in this way the effect of nitrogen monoxide (NO) that forms continuously in the human organism is, as a matter of fact, amplified since the cGMP activates the NO synthase enzyme producing the nitrogen monoxide. The higher amount of the produced nitrogen monoxide results in both vasodilation and an enhanced therapeutical width of the active ingredients having the effect of digitalis.

In the description and claims, under an „active ingredient having the effect of digitalis" glycosides that can be obtained from plants of the Digitalis family (e.g. Digitalis purpurea, Digitalis lanata, Digitalis lutea etc.) or digitaloides i.e. glycosides of similar effect which can be obtained from plants of the Strophantus family (e.g. Strophantus gratus, Strophantus kombé etc.) or from other plants (e.g. Scilla maritima,

Convallaria majalis etc.) are meant. The term „glycosides" includes a pure glycoside, a mixture of glycosides as well as products that can be prepared by the chemical transformation of said glycosides. Examples of the active ingredient having the effect of digitalis are digoxin, digitoxin, lanatoside A, lanatoside B, lanatoside C, lanatoside D, K-strophanthin, G-strophanthin (ouabain), scillaren, convallatoxin etc.

Preferred active ingredients having the effect of digitalis are digoxin, digitoxin and ouabain.

Under a „cyclic guanosine monophosphate (cGMP) phosphodiesterase inhibitor" an agent inhibiting the metabolism of the cyclic guanosine monophosphate is meant. As a matter of fact, said agent inhibits the various isoenzymes of cGMP phosphodiesterase. The task of these isoenzymes is to decompose cGMP.

Examples of the cGMP phosphodiesterase inhibitors are the following ones:

cicletanine [chemical name: (±)-3-(4-chlorophenyl)-1,3-dihydro-6-methylfuro-[3,4-c]pyridin-7-ol] or a pharmaceutically suitable acid addition salt thereof, a known antihypertensive [US-P No. 4,383,998],

vinpocetine [chemical name: (3α,16α)-eburnamenine-14-carboxylic acid ethyl ester], a known cerebral vasodilator [US-P No. 4,035,370],

sildenafil [chemical name: 1-[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl-sulfonyl]-4-methylpiperazine] or a pharmaceutically suitable

acid addition salt thereof, a known active agent for the treatment of impotence,
zaprinast [chemical name: 1,4-dihydro-5-(2-propoxyphenyl)-7*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-one] or a pharmaceutically suitable acid addition salt thereof, a known antiallergic,
ibudilast [chemical name: 2-methyl-1-[2-(1-methylethyl)-pyrazolo[1,5-a]pyridin-3-yl]-1-propanone] or a pharmaceutically suitable acid addition salt thereof, a known antiallergic, antiasthmatic and vasodilator [US-P No. 3,850,941],
rolipram [chemical name: 4-[3-cyclopentyloxy)-4-(methoxy-phenyl)]-2-pyrrolidinone] or a pharmaceutically suitable acid addition salt thereof, a known antidepressant [US-P No. 4,193,926],
pimobendan [chemical name: 4,5-dihydro-6-[2-(4-methoxy-phenyl)-1*H*-benzimidazol-5-yl]-5-methyl-3(2H)-pyridazinone] or a pharmaceutically suitable acid addition salt thereof, a known cardiotonic [US-P No. 4,361,563],
vesnarinone [chemical name: 1-(3,4-dimethoxybenzoyl)-4-(1,2,3,4-tetrahydro-2-oxo-6-quinolinyl)-piperazine] or a pharmaceutically suitable acid addition salt thereof, a known cardiotonic [US-P No. 4,415,572],
ODQ [chemical name: 1*H*-[1,2,4]oxadiazolo[4,3-a]quinoxaline-1-one] or a pharmaceutically suitable acid addition salt thereof,
WIN-58237 [chemical name: 1-cyclopentyl-3-methyl-6-(4-pyridyl)pyrazolo[3,4-d]pyrimidin-4-(5H)-one] or a pharmaceutically suitable acid addition salt thereof, ,
ONO-1505 [chemical name: 4-[2-(2-hydroxyethoxy)ethyl-

amino]-2-(1H-imidazol-1-yl)-6-methoxyquinazoline methane sulfonate] and
DMPPO [1,3-dimethyl-6-(2-propoxy-5-methanesulfonylamido-phenyl)pyrazolo[3,4-d]pyrimidin-4-(5*H*)-one] or a pharmaceutically suitable acid addition salt thereof.

Preferred cGMP phosphodiesterase inhibitors of the invention are the following ones: cicletanine or a pharmaceutically suitable acid addition salt thereof, vinpocetine, sildenafil or a pharmaceutically suitable acid addition salt thereof and zaprinast or a pharmaceutically suitable acid addition salt thereof. An especially preferred cGMP phosphodiesterase inhibitor of the invention is cicletanine or a pharmaceutically suitable acid addition salt thereof, suitably the hydrochloride.

The pharmaceutical composition of the invention comprises the active ingredient having the effect of digitalis and the cGMP phosphodiesterase inhibitor, in general, in a weight ratio of (1-500)-(500-1), preferably (1-200):(200-1). If desired and chemically possible, the active ingredient having the effect of digitalis or the cGMP phosphodiesterase inhibitor can be present in the pharmaceutical composition of the invention in the form of a pharmaceutically suitable acid addition salt or a salt formed with a pharmaceutically suitable base thereof. Generally, the pharmaceutical composition of the invention is a solid or liquid preparation suitable for peroral or parenteral administration.

The solid pharmaceutical compositions suitable for peroral

administration may be powders, capsules, tablets, film-coated tablets, microcapsules etc., and can comprise binding agents such as gelatine, sorbitol, poly(vinylpyrrolidone) etc.; filling agents such as lactose, glucose, starch, calcium phosphate etc.; auxiliary substances for tabletting such as magnesium stearate, talc, poly(ethylene glycol), silica etc.; wetting agents such as sodium laurylsulfate etc. as the carrier.

The liquid pharmaceutical compositions suitable for peroral administration may be solutions, suspensions or emulsions and can comprise e.g. suspending agents such as gelatine, carboxymethylcellulose etc.; emulsifiers such as sorbitane monooleate etc.; solvents such as water, oils, glycerol, propylene glycol, ethanol etc.; preservatives such as methyl p-hydroxybenzoate etc. as the carrier.

Pharmaceutical compositions suitable for parenteral administration consist of sterile solutions of the active ingredient, in general.

The pharmaceutical composition of the invention is prepared by admixing the active ingredient to one or more carrier(s), and converting the mixture obtained to a pharmaceutical composition in a manner known *per se*. Dosage forms listed above as well as other dosage forms and the preparation thereof, furthermore the useful carriers are known from the literature, see e.g. Remington's Pharmaceutical Sciences, 18th Edition, Mack Publishing Co., Easton, USA (1990). The pharmaceutical composition contains dosage unit, in general.

A preferred pharmaceutical composition of the invention contains an active ingredient having the effect of digitalis, for example digoxin, and cicletanine, vinpocetine, sildenafil, zaprinast, ibudilast, rolipram, pimobendan, vesnarinone, ODQ, WIN-58237, ONO-1505 or DMPPO or, if desired and chemically possible, a pharmaceutically suitable acid addition salt or a salt formed with a pharmaceutically suitable base thereof in addition to one or more conventional carrier(s).

An especially preferred pharmaceutical composition of the invention contains an active ingredient having the effect of digitalis, for example digoxin, and cicletanine, vinpocetine, sildenafil, zaprinast or if desired and chemically possible, a pharmaceutically suitable acid addition salt or a salt formed with a pharmaceutically suitable base thereof in addition to one or more conventional carrier(s).

A most preferred pharmaceutical composition of the invention contains digoxin and cicletanine or cicletanine hydrochloride in addition to one or more conventional carrier(s).

The favourable therapeutical effect of the pharmaceutical composition of the invention was studied in the following tests.

1) Determination of the 50 % maximum positive inotropic effect and the „torsade de pointes" ventricular tachycardia in rabbits.

The animals were pretreated with 5 mg/kg of atropine intravenously. Ouabain was then applied as an intermittent infusion i.e. an initial dose of 20 μg/kg of ouabain was infused

over 4 minutes i.v. This was followed by an interval lasting for 26 minutes, then 10 μg/kg of ouabain was infused in every 10th minute until the onset of „torsade de pointes" ventricular tachycardia (TdP). These experiments were carried out after an intravenous bolus of 10 mg/kg or 30 mg/kg of cicletanine or a placebo injection used as a control. Each group of animals consisted of 6 rabbits. Total ouabain doses to produce half maximum positive inotropic effect (dP/dt_{50}) and those eliciting TdP are given in Table I.

Table I

Active ingredient used for the treatment	Ouabain dose in μg/kg to produce dP/dt_{50}	Ouabain dose in μg/kg to elicit TdP
Ouabain (control)	49	125
Ouabain +10 mg/kg of cicletanine	30	198
Ouabain +30 mg/kg of cicletanine	26	195

From Table I it is evident that in the cardiotonic therapy 49 μg/kg of ouabain has to be administered to achieve 50 % of maximum positive inotropic effect. When cicletanine was also administered, as low as about 60 % of the control value (i.e. 26

to 30 μg/kg of ouabain) was sufficient to produce the above effect.

From Table I it can be also seen that the unfavourable side-effect of the cardiotonic therapy carried out with ouabain i.e. the ventricular tachycardia appeared at a much higher dose of ouabain in the presence of cicletanine than in the absence of cicletanine.

2) Effect of cicletanine on the safety margin of ouabain in guinea pigs.

An intravenous bolus of 10 or 30 mg/kg of cicletanine was administered to the test groups each of which consisted of 10 guinea pigs. The animals were anaesthetized with an intraperitoneal injection of 30 mg/kg of pentobarbital sodium. The animals were pretreated with atropine (1.0 mg/kg i.p.) as well. Subsequently, ouabain was infused intermittently. An initial dose of 60 μg/kg of ouabain was infused over a period of 5 minutes followed by an interval lasting for 30 minutes. 30 μg/kg of ouabain was then infused in every 10^{th} minute until cardiac arrest. Under these conditions, various types of rhythm disturbances occured in the following order of sequence: solitary ventricular ectopic beats, bigeminy (BG), accelerated indioventricular rhythm (AIVR), ventricular tachycardia (VT), ventricular fibrillation (VF), and finally cardiac arrest. The cumulative ouabain doses required to produce BG, AIVR, VT and VF in the absence and presence of cicletanine are given in Table 2.

Table 2

Active ingredient used for the treatment	Ouabain dose in μg/kg to produce BG	Ouabain dose in μg/kg to produce AIVR	Ouabain dose in μg/kg to produce VT	Ouabain dose in μg/kg to produce VF
Ouabain (control)	125	190	240	315
Ouabain +10 mg/kg of cicletanine	175	255	320	415
Ouabain +30 mg/kg of cicletanine	180	270	330	440

From Table 2 it can be seen that the unfavourable side-effects of the cardiotonic therapy carried out with ouabain appeared at much higher doses in the presence of cicletanine than in the absence of cicletanine in guinea pigs, too.

The results of the above tests indicate that the cGMP phosphodiesterase inhibitors enhance the therapeutical width of digitalis glycosides as shown by the reduction of the dose required for cardiotonic therapy and the increase of dose eliciting arrhythmogenic side-effects.

The invention includes a use of a cGMP phosphodiesterase inhibitor for the preparation of a pharmaceutical composition enhancing the therapeutical width of an active ingredient having the effect of digitalis. When such a pharmaceutical composition is administered to a patient being treated with an active ingredient having the effect of digitalis, the aim of the invention i.e. the enhanced therapeutical width of the active ingredient having the effect of digitalis is also achieved.

Furthermore, the invention includes a method for enhancing the therapeutical width of an active ingredient having the effect of digitalis in which a patient being in need of a cardiotonic treatment with an active ingredient having the effect of digitalis is treated, in addition to the active ingredient having the effect of digitalis, also with a cGMP phosphodiesterase inhibitor.

The daily dose of the active ingredient having the effect of digitalis e.g. digoxin is usually 0.05 to 0.75 mg for an adult person, while the daily dose of the cGMP phosphodiesterase inhibitor such as cicletanine hydrochloride is, in general, 1 to 100 mg/kg body weight, preferably 1 to 20 mg/kg.

The invention is further illustrated by means of the following Examples.

Example 1

Preparation of hard gelatine capsules

One capsule contains 0.07 mg of digoxin, 200 mg of cicletanine hydrochloride and 250 mg of microcrystalline cellulose. The ingredients are mixed and filled into hard gelatine capsules.

Example 2

Preparation of tablets

One tablet contains 0.1 mg of digoxin, 400 mg/kg of cicletanine hydrochloride, 9.9 mg of silica, 50 mg of carboxy-methyl cellulose, 30 mg of microcrystalline cellulose and 10 mg of magnesium stearate. The ingredients are admixed and compressed to tablets of 0.5 g.